D14 cont'd

135. (New) The method of claim 75, wherein said method further comprises comparing said change in signal detected in step (iii) with a change in signal detected in a second control cell line lacking said GPCR detected under the same conditions as in step (iii).

Cont'd E16

136. (New) The method of claim 81, wherein said method further comprises comparing said change in reporter gene expression detected in step (ii) with a change in reporter gene expression detected in a second control cell line lacking said GPCR detected under the same conditions as in step (ii).

137. (New) The method of claim 90, wherein said method further comprises comparing said change in reporter gene expression detected in step (c) with a change in signal detected in a second control cell line lacking said GPCR detected under the same conditions as in steps (b) and (c).

138. (New) The method of claim 94, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a second control cell line lacking said GPCR detected under the same conditions as in steps (i), (ii) and (iii).--

REMARKS

WITHDRAWAL OF CERTAIN REJECTIONS

Applicants acknowledge that certain of the previous rejections of claims 63-109 under 35 USC §112 first paragraph, and second paragraphs have been withdrawn, and that all of the rejections under 35 USC §103(a) have been withdrawn.

AMENDMENTS

Claims 63 to 123 were pending in the instant application prior to the instant amendment. Applicants have canceled claims 64, 65, 72, 73, 76, 77, 82, 83, 91, 92, 95, 96, 103 and 104, and added an equal number of new claims (124 to 138). Claims 63, 67,

71, 75, 79, 81, 85, 89, 90, 94, 98, 102, 106, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122 and 123 have been amended.

Claims 63, 71, 75, 81, 90, 94, and 102 have been amended by replacement of the term "having at least 70 % sequence homology to SEQ. ID. NO. 2.," with the term "having at least 95 % sequence homology to SEQ. ID. NO. 2." These amendments are fully supported throughout the specification, and do not introduce new matter. Specific support is found, for example, on page 17, last paragraph.

These claims have also been amended by deletion of the term "expressing a putative GPCR in a cell", by the term "providing a cell," and by the insertion of the term "functional" immediately in front of the term "Gα15 protein". These amendments are fully supported throughout the specification, and do not introduce new matter.

Additionally these claims have been amended by insertion of the term "wherein said GPCR is not naturally expressed in said cell." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example in original claims 65, 73, 77, 83, 92, 96 and 104.

Claims 63, 81, 94 and 102, have been amended by insertion of the term " a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example in original claims 64, 72, 76, 82, 91, 95 and 103.

Claims 71, 75 and 90 have been amended by insertion of the term " a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example in original claims 64, 72, 76, 82, 91, 95 and 103.

Claims 67, 85, 98, 106 have been amended by deletion of the term "further comprising contacting said cell with a reporter gene substrate," and insertion of the term "wherein said reporter gene is selected from the group consisting of luciferase, GFP, chloroamphenical acetyl transferase, β-galactosidase, β-lactamase and secreted alkaline phosphatase." This amendment is fully supported throughout the specification, and does

not introduce new matter. Specific support is found, for example on page 15, lines 6 to 13 of the present specification.

Claims 110, 112, 114 and 116 have been amended by deletion of the term "wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2" and by insertion of the phrase "further comprising contacting said cell with a reporter gene substrate." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example in originally filed claims 67, 85, 98 and 106.

Claims 111, 113, 115 and 117 have been amended by deletion of the term "Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2" and by insertion of the phrase "reporter gene is β-lactamase." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example on page 19, lines 26 to 31 of the present specification.

Claims 118, 119, 120 and 121 have been amended by deletion of the term "Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2," and by insertion of the phrase "reporter gene substrate is CCF2." This amendment is fully supported throughout the specification, and does not introduce new matter.

Claim 122 and 123 have been amended by deletion of the term "Gα15 protein has at least 95% sequence homology to SEQ. ID. NO. 2," and by insertion of the term "GPCR is selected from the group consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors." This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example on page 21 of the present specification.

Additionally new claims 124 to 138 have been added.

New claims 124 and 125 are directed to the methods of claim 90 and 94, wherein the GPCR is selected from consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors. This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example on page 21 of the present specification.

New claims 126 to 128 are directed to embodiments of the claimed methods wherein the intracellular calcium indicator is Fura II. This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example on page 27, lines 14 to16 of the present specification.

New claims 129 to 132 are directed to embodiments of the claimed methods wherein the second heterologous promoter is NFAT. This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example on the last two lines of page 20 of the present specification.

New claims 133 to 138 are directed to certain embodiments of the claimed methods in which the method includes an additional step of comparing the change in reporter gene expression, or signal transduction in the cell comprising a GPCR with the change reporter expression, or signal transduction in a control cell line lacking the GPCR. This amendment is fully supported throughout the specification, and does not introduce new matter. Specific support is found, for example, in claim 34 as originally filed.

Attached hereto as Appendix A is a marked up version of the changes made to the claims by the current amendments. No new matter has been added.

Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

REJECTION OF CLAIMS 63 TO 109 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Maintained claim rejections

The Examiner rejects claims 63 to 123 under 35 U.S.C. §112, first paragraph, because "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims."

Specifically, the Examiner is of the opinion that "due to the lack of guidance and working examples of what amino acid residues are critical to maintain the function of a

Gα15 other than SEQ. ID:2, it is unpredictable to the artisan of how to make a functional Gα15 of SEQ. ID:2."

Applicants respectfully traverse the foregoing rejection on the grounds that the claimed invention is fully enabled by the disclosure in Applicant's specification. As recited in the response filed August 27, 2001, the Examiners position in effect imposes an additional requirement, of a working example or examples to enable the breadth of the claims. Applicants assert that in fact, 35 USC § 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it".

Accordingly, it is Applicants' position that based on the teachings of the specification, which the Examiner acknowledges enables the claimed methods with the disclosed SEQ. ID. NO.2, the ordinarily skilled artisan would be able to make and practice the claimed methods with Gα15 proteins that contained similar sequences with no more than routine experimentation. However to expedite the allowance of the present application, Applicants have amended the currently pending claims to explicitly recite a *functional* Gα15 protein having at least 95 %, sequence homology to SEQ ID NO. 2.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 63 to 123 under 35 U.S.C. § 112, first paragraph.

New claim rejections under 35 U.S.C. §112, first paragraph

A. The Examiner newly rejects claims 63, 71, 75, 81, 90, 94 and 102 under 35 U.S.C. §112, first paragraph, because "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention."

Specifically, the Examiner is firstly of the opinion that "the claims do not recite that the GPCR has to be transfected into the cell," and that "[a]pplicants have not taught the artisan how to identify a ligand to a specific endogenously expresses GPCR."

Secondly the Examiner is of the opinion that "the way the claims have been written it appears that the Gα15 protein is able to direct[l]y cause the activation of a reporter gene."

Applicants respectfully traverse the foregoing rejection on the grounds that a person of ordinary skill in the relevant art, *i.e. in this technical field,* would immediately recognize how to make and use the claimed inventions without due experimentation. Specifically a person of ordinary skill in this specific art would recognize that appropriate controls would typically be required to confirm that a ligand, or test chemical was acting on a specific receptor, whether endogenously, or exogenously expressed in the cell.

However in order to expedite the allowance of the present application, Applicants have amended the claims to clarify the claimed subject matter, by including the term "wherein said GPCR is not naturally expressed in said cell," and by including language in the claim that recites that the cell comprises a second or third heterologous promoter operably linked to a polynucleotide encoding the GPCR. Applicant's according request withdrawal of this rejection.

Applicants respectfully submit that the question of whether the Gα15 protein is able to directly, or indirectly cause the activation of the reporter gene is not relevant to the question of enablement. Rather the critical point is that activation of the Gα15 protein by a GPCR is sufficient to accomplish the modulation of reporter gene expression, and therefore meets the quoted objective of the claims. Applicants are not responsible for the correctness of theories as to how Gα15 activation is capable of modulating the expression of the reporter gene. The correctness of such theories or explanations is not related to validity of the claims under consideration. See e.g. Fromson v. Advance Plate., Inc., 720 F. 2d 1565 (Fed. Cir. 1983). Applicants accordingly request withdrawal of this rejection of the claims.

REJECTION OF CLAIMS 63-109 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

A. The Examiner rejects claims 63, 64, 66-72, 74 – 76, 78-82, 84-91, 93-95, 97-103 and 105-123 under 35 U.S.C. §112 second paragraph because the Examiner alleges that the claims are confusing "since it appears that, even though the claims appear to imply that the GPCR, reporter gene and Gα15 are not endogenously expressed in the cell, the claims are not limited to transfected cells and read on cells which endogenously express any or all of these components."

Applicants respectfully traverse the foregoing rejection on the grounds that the claims as originally written are clear and not confusing to one of ordinary skill in the art.

However in order to expedite the allowance of the present application, Applicants have amended the claims to clarify the claimed subject matter, by including the term "wherein said GPCR is not naturally expressed in said cell," and by including language in the claim that the cell comprises a second or third heterologous promoter operably linked to a polynucleotide encoding the GPCR. Applicant's according request withdrawal of this rejection. Accordingly Applicants respectfully request withdrawal of the rejection.

Further the Examiner argues that for the embodiments in which the GPCR is endogenously expressed, the claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. Applicants respectfully traverse the rejection, and submit that the rejection is no longer applicable to the claims as amended. Accordingly Applicants request withdrawal of the rejection.

B. The Examiner rejects claims 67-70, 74, 78, 80, 84-88, 93, 97-101 and 105-109 under 35 U.S.C. §112 because the Examiner alleges that "it is not clear at what time point in the method steps these additional steps are performed."

Applicants respectfully traverse the rejection, on the grounds that a person of ordinary skill in the respective art would clearly be able to devise a time point at which at which the comparison steps could be performed. Such time course studies are routinely performed, and discussed in standard text books, as well as research publications that were publicly available at the time the present application was filed. Furthermore the specification provides extensive guidance, as to appropriate time points for measuring GPCR activation.

Specifically, for signal transduction measurements (relevant to independent claims 71, 75 and 90) the specification exemplifies appropriate time courses for calcium mobilization, for example 20 to 60 seconds after addition of the ligand or test chemical., (see page 43). For reporter gene assays, the specification again exemplifies appropriate time courses for measuring changes in gene expression, for example 90 to 120 minutes after addition of the ligand or test chemical (see page 20). According it was well within the knowledge of the art in this technical field to know, or easily determine suitable time

points for making the required comparisons. These studies are routinely conducted by scientists familiar with the use of cell based assays for drug discovery. Applicants accordingly request withdrawal of this rejection.

Additionally, the Examiner is of the opinion that "it is not clear what a "reporter gene substrate" is, or how contacting the cell with said substrate, or with the compounds of claims 68-70, 78, 80, 84-88, 93, 97-101 and 105-109 will provide the necessary information regarding the relationship between the GPCR, ligand and / or test compound or chemical."

Applicants respectfully traverse the rejection, on the grounds that a person of ordinary skill in the art would be familiar with, or could readily identify suitable reporter gene substrates for use with the reporter genes disclosed in the specification. Such reporter gene substrates, and appropriate protocols for their use, were well know as of the filing date of the present specification. According a person of ordinary skill in the art would readily recognize what a reporter gene substrate is, and how to use it in the claimed methods. As further evidence to this fact, Applicants enclose hereto marked as Exhibit A, copies of various patents and publications describing various reporter gene substrates, and their use.

Goldsmith *et al.*, J. Biol. Chem. **264** No. 29 17190-17197 (1989) describes reporter gene and signal transduction cell based assays incorporating the use of a heterologously expressed muscarinic receptor to define the role of various calmodulin mutants in the signal transduction process. The paper describes both calcium measurements and reporter gene studies.

US Patent No. 5,401,629 entitled " Assay methods and compositions useful for measuring the transduction of an intracellular signal," describes the use of cell-based assays for screening for GPCR and ion channel agonists and antagonists. The patent describes transcriptional assays for GPCR and ion channel activation and their use for drug discovery. The patent also describes the creation of control cell lines, lacking the heterologously expressed GPCR.

Chen *et al.*, Analytical Biochemistry **226** 349-354 (1995) describes the development of reporter gene assays for GPCRs coupled to either Gα s or Gq. The

article describes the creation of cell lines expressing heterologously expressed GPCRs, time course studies for reporter gene expression and the use of appropriate controls.

The Molecular probes catalog, sixth edition (1996), Chapter 10, describes in detail a large number of reporter gene substrates, and their use for cell based assays. The chapter describes various substrates for measuring glycosidases, phosphatases and a range of other activities.

Thus the state of the art is significantly higher than that characterized by the Examiner, accordingly a person of ordinary skill in the art, having read Applicants specification, and being in possession of the knowledge of the art, would have no difficulty in establishing suitable controls to determine receptor specificity, identify appropriate times for conducting time course studies, and the use of appropriate substrates for each reporter enzyme. Accordingly Applicants respectfully request withdrawal of the rejection.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 102-123. Applicants further submit that the rejection is not applicable to new claims 124-138. In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. Please apply any charges not covered, or any credits, to Deposit Account 07-1895.

Respectfully submitted,

Date_____

_____

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EXHIBIT A

APPENDIX A

63. (Twice amended) A method of identifying a G-protein coupled receptor (GPCR) for a given ligand, the method comprising:

(i) [expressing a putative GPCR in] providing a cell, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least [70] 95 % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR,

wherein said GPCR is not naturally expressed in said cell, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein[,];

(ii) contacting said cell with said ligand; and

(iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand.

64. (Canceled)

65. (Canceled)

66. The method of claim 63, wherein said GPCR is a taste receptor.

67. (Amended) The method of claim [66] 63, [further comprising contacting said cell with a reporter gene substrate] wherein said reporter gene is selected from the group consisting of luciferase, GFP, chloramphenical acetyl transferase, β-galactosidase, β–lactamase and secreted alkaline phosphatase.

68. The method of claim 63, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

69. The method of claim 68, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

70. The method of claim 68, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

71. (Twice amended) A method for identifying a GPCR for a given ligand, the method comprising:

i) [expressing a putative GPCR in] providing a cell, said cell comprising,

a first heterologous promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least [70] 95 % sequence homology to SEQ. ID. NO. 2, and

a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein, and

wherein said GPCR is not naturally expressed in said cell;

ii) contacting said cell with said ligand; and

iii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said ligand with said signal after addition of said ligand,

wherein said signal transduction detection system comprises a dye.

72. (Canceled)

73. (Canceled)

74. The method of claim 71, wherein said signal transduction detection system comprises an intracellular calcium indicator.

75. (Amended) A method of [a] identifying [of] a ligand for a GPCR, the method comprising:

i) contacting a cell with a test chemical, said cell comprising

a first heterologous promoter operably linked to a first polynucleotide encoding a <u>functional</u> Gα15 protein having at least [70] <u>95</u> % sequence homology to SEQ. ID. NO. 2,

<u>a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,</u>

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein,

<u>wherein said GPCR is not naturally expressed in said cell</u>;

ii) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical,

wherein said signal transduction detection system comprises a dye.

76. (Canceled)

77. (Canceled)

78. The method of claim 75, wherein said signal transduction detection system comprises an intracellular calcium indicator.

79. (Twice amended) The method of claim 75, further comprising comparing a signal from a first plurality of cells in the presence of said test chemical with either:

i) a signal from a second plurality of cells in the presence of said test chemical, wherein said second plurality of cells lack <u>said Gα15 protein</u> [either a promiscuous Gα protein, a target protein] or

ii) a signal from said first plurality of cells in the absence of said test chemical.

80. The method of claim 75, wherein said detecting comprises fluorescence detection.

81. (Twice amended) A method of [a] identifying [of] a ligand for a GPCR, the method comprising;

i) contacting a cell with a test chemical, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a <u>functional</u> Gα15 protein having at least [70] <u>95</u> % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

<u>c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,</u>

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR,

<u>wherein said GPCR is not naturally expressed in said cell</u>, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein;

ii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said ligand with reporter gene expression after addition of said ligand.

82. (Canceled)

83. (Canceled)

84. The method of claim 81, wherein said detecting comprises fluorescence detection.

85. (Amended) The method of claim 81, [further comprising contacting said cell with a reporter gene substrate] wherein said reporter gene is selected from the group consisting of luciferase, GFP, chloramphenical acetyl transferase, β-galactosidase, β–lactamase and secreted alkaline phosphatase.

86. The method of claim 81, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

87. The method of claim 86, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

88. The method of claim 81, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

89. (Twice amended) The method of claim 81, further comprising comparing a signal from a first plurality of cells in the presence of said test chemical with either:

i) a signal from a second plurality of cells in the presence of said test chemical, wherein said second plurality of cells lack said Gα15 protein [either a promiscuous Gα protein, a target protein], or

ii) a signal from said first plurality of cells in the absence of said test chemical.

90. (Twice amended) A method for identifying a modulator of signal transduction mediated by GPCR activation in a cell, the method comprising:

a) contacting a cell with a test chemical, said cell comprising,

a first heterologous promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least [70] 95 % sequence homology to SEQ. ID. NO. 2, and

a second heterologous promoter operably linked to a second polynucleotide encoding said GPCR,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR and wherein said GPCR is normally coupled to either $G\alpha_i$, $G\alpha_s$ or $G\alpha_{12}$ in the absence of said Gα15 protein, and

wherein said GPCR is not naturally expressed in said cell;

b) contacting said cell with a ligand that, in the absence of [the] said test chemical, activates signal transduction via said GPCR in said cell, and

c) detecting a change in a signal with a signal transduction detection system by comparing said signal prior to addition of said test chemical with said signal after addition of said test chemical.

91. (Canceled)

92. (Canceled)

93. The method of claim 90, wherein said signal transduction detection system comprises an intracellular calcium indicator.

94. (Twice amended) A method for identifying a modulator of signal transduction in a cell, the method comprising:

i) contacting a cell with a test chemical, said cell comprising,

a) a first heterologous promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least [70] 95 % sequence homology to SEQ. ID. NO. 2,

b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, and

wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein, and wherein said GPCR is not naturally expressed in said cell;

ii) [contacting said cell with a test chemical;] contacting said cell with a ligand that, in the absence of said test chemical activates signal transduction via said GPCR in said cell; and

iii) detecting a change in reporter gene expression by comparing reporter gene expression prior to addition of said test chemical with reporter gene expression after addition of said test chemical.

95. (Canceled)

96. (Cancelled)

97. The method of claim 94, wherein said detecting comprises fluorescence detection.

98. (Amended) The method of claim 94, [further comprising contacting said cell with a reporter gene substrate] wherein said reporter gene is selected from the group consisting of luciferase, GFP, chloramphenical acetyl transferase, β-galactosidase, β–lactamase and secreted alkaline phosphatase.

99. The method of claim 94, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

100. The method of claim 99, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

101. The method of claim 94, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

102. (Twice amended) A method of functionally profiling a test chemical comprising the steps of.

i) contacting a panel of cells with a test chemical, said panel of cells comprising, a plurality of cell clones, each cell clone comprising,

[a) a GPCR,]

[b)] a) a first heterologous promoter operably linked to a first polynucleotide encoding a functional Gα15 protein having at least [70] 95 % sequence homology to SEQ. ID. NO. 2,

[c)] b) a second heterologous promoter operably linked to a second polynucleotide encoding a reporter gene,

c) a third heterologous promoter operably linked to a third polynucleotide encoding said GPCR,

wherein said cell stably expresses said Gα15 protein at sufficient levels to permit promiscuous coupling to said GPCR, wherein said second heterologous promoter is directly or indirectly modulated by the activity of said Gα15 protein,

wherein said GPCR is not naturally expressed in said cell, and

wherein each cell clone differs only with respect to [the] said GPCR that is expressed[,];

ii) contacting said cell clones with a test chemical;

iii) detecting reporter gene expression from said cell clones

iv) comparing reporter gene expression between said cell clones.

103. (Canceled)

104. (Canceled)

105. The method of claim 102, wherein said detecting comprises fluorescence detection.

106. (Amended) The method of claim 102, [further comprising contacting said cell with a reporter gene substrate] wherein said reporter gene is selected from the group consisting of luciferase, GFP, chloramphenical acetyl transferase, β-galactosidase, β–lactamase and secreted alkaline phosphatase.

107. The method of claim 102, further comprising contacting said cell with a compound that increases calcium levels inside said cell.

108. The method of claim 107, wherein said compound is selected from the group consisting of ionomycin and thapsigargin.

109. The method of claim 107, further comprising contacting said cell with phorbol myristate acetate or an analog thereof.

110. (Amended) The method of claim [63] 67, [wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] further comprising contacting said cell with a reporter gene substrate.

111. (Amended) The method of claim [71] 67, wherein said [Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] reporter gene is β–lactamase.

112. (Amended) The method of claim [75] 85, [wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] further comprising contacting said cell with a reporter gene substrate.

113. (Amended) The method of claim [81] 85, wherein said [Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] reporter gene is β–lactamase.

114. (Amended) The method of claim [90] 98, [wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] further comprising contacting said cell with a reporter gene substrate.

115. (Amended) The method of claim [94] 98, wherein said [Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] reporter gene is β–lactamase.

116. (Amended) The method of claim [102] 106, [wherein said Gα15 protein has at least 80 % sequence homology to SEQ. ID. NO. 2] further comprising contacting said cell with a reporter gene substrate.

117. (Amended) The method of claim [63] 106, wherein said [Gα15 protein has at

least 95 % sequence homology to SEQ. ID. NO. 2] reporter gene is β–lactamase.

118. (Amended) The method of claim [71] 110, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2] reporter gene substrate is CCF2.

119. (Amended) The method of claim [75] 112, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2] reporter gene substrate is CCF2.

120. (Amended) The method of claim [81] 114, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO:. 2] reporter gene substrate is CCF2.

121. (Amended) The method of claim [90] 116, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2] reporter gene substrate is CCF2.

122. (Amended) The method of claim [94] 75, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2] GPCR is selected from the group consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

123. (Amended) The method of claim [102] 81, wherein said [Gα15 protein has at least 95 % sequence homology to SEQ. ID. NO. 2] GPCR is selected from the group consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

Please add new claims 124 to 138 as below:

124. (New) The method of claim 90, wherein said GPCR is selected from the group consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

125. (New) The method of claim 94, wherein said GPCR is selected from the group consisting of muscarinic receptors, nictonic acetylcholine receptors, GABA receptors, glutamate receptors, adrenergic receptors, dopamine receptors and serotonin receptors.

126. (New) The method of claim 74, wherein said intracellular calcium indicator is Fura II.

127. (New) The method of claim 78, wherein said intracellular calcium indicator is Fura II.

128. (New) The method of claim 93, wherein said intracellular calcium indicator is Fura II.

129. (New) The method of claim 63, wherein said second heterologous promoter is NFAT.

130. (New) The method of claim 81, wherein said second heterologous promoter is NFAT.

131. (New) The method of claim 94, wherein said second heterologous promoter is NFAT.

132. (New) The method of claim 102, wherein said second heterologous promoter is NFAT.

133. (New) The method of claim 63, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a second control cell line lacking said GPCR detected under the same conditions as in step (iii).

134. (New) The method of claim 71, wherein said method further comprises comparing said change in signal detected in step (iii) with a change in signal detected in a second control cell line lacking said GPCR detected under the same conditions as in step (iii).

135. (New) The method of claim 75, wherein said method further comprises comparing said change in signal detected in step (iii) with a change in signal detected in a second control cell line lacking said GPCR detected under the same conditions as in step (iii).

136. (New) The method of claim 81, wherein said method further comprises comparing said change in reporter gene expression detected in step (ii) with a change in reporter gene expression detected in a second control cell line lacking said GPCR detected under the same conditions as in step (ii).

137. (New) The method of claim 90, wherein said method further comprises comparing said change in reporter gene expression detected in step (c) with a change in signal detected in a second control cell line lacking said GPCR detected under the same conditions as in steps (b) and (c).

138. (New) The method of claim 94, wherein said method further comprises comparing said change in reporter gene expression detected in step (iii) with a change in reporter gene expression detected in a second control cell line lacking said GPCR detected under the same conditions as in steps (i), (ii) and (iii).